ORIGINAL RESEARCH

Comparing Medication Adherence and Persistence Among Patients with Type 2 Diabetes Using Sodium-Glucose Cotransporter 2 Inhibitors or Sulfonylureas

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BACKGROUND: Patients with type 2 diabetes treated with pharmacotherapy should be adherent to and persistent with their medications to experience glycemic control and prevent associated complications.

OBJECTIVE: To compare medication adherence and persistence among patients with type 2 diabetes who are newly initiating a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a sulfonylurea.

METHODS: This was a retrospective, observational cohort study using the MarketScan claims databases. The patients who were selected for the study had newly initiated treatment with an SGLT-2 inhibitor or a sulfonylurea between January 1, 2015, and December 31, 2015 (index date; class of earliest medication is defined as the index class); were aged ≥18 years on the index date; were continuously enrolled with health insurance for 12 months before and 6 months after (ie, follow-up) the index date; and had ≥1 baseline diagnoses of type 2 diabetes. Study exclusions were type 1 diabetes, pregnancy, and gestational diabetes. Medication adherence was measured by the proportion of days covered (PDC) with the index class during the follow-up period and dichotomized as adherent (PDC ≥80%) or nonadherent. Persistence was defined as the number of days from the index date until a >60-day continuous gap in days without the index drug class (ie, discontinuation) or the end of follow-up. A propensity score model was used to match patients receiving an SGLT-2 inhibitor to patients receiving a sulfonylurea in a 1:1 ratio based on patient characteristics. Logistic (ie, adherence) and Cox (ie, persistence) regression models were fit to the matched samples.

RESULTS: Initially, the study included 17,724 patients who received an SGLT-2 inhibitor and 25,490 patients who received a sulfonylurea. After propensity score matching, 13,657 patients remained in each cohort. Compared with patients receiving a sulfonylurea, a statistically significantly greater percentage of patients receiving an SGLT-2 inhibitor were adherent to therapy (61.4% vs 53.9%, respectively; odds ratio of adherence, 1.364; 95% confidence interval [CI], 1.30-1.43; *P* <.001) and persistent (76.1% vs 68.9%, respectively; hazard ratio of discontinuation, 0.746; 95% CI, 0.71-0.78; *P* <.001).

CONCLUSION: Maintaining adherence to and persistence with antidiabetes medication is vital to glycemic control among patients with type 2 diabetes. In this real-world study, patients who newly initiated treatment with SGLT-2 inhibitors were more likely to adhere to treatment and persist with the initiated therapy than similar patients who newly initiated treatment with sulfonylureas.

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KEY WORDS: adherence, antidiabetes medication, glycemic control, persistence, SGLT-2 inhibitor, sulfonylureas, type 2 diabetes

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Type 2 diabetes mellitus is a chronic disease that affects more than 29 million individuals in the United States.[1] Patients with type 2 diabetes have insulin resistance, a condition in which the body does not produce enough insulin to maintain normal levels of blood glucose.[2] Prolonged elevated blood glucose, typically measured as glycated hemoglobin (HbA_{1c}),

KEY POINTS

- It is well-known that maintaining adherence to antidiabetes medications is vital to glycemic control.
- This is the first real-world study using claims data to compare adherence and persistence between patients receiving SGLT-2 inhibitors or sulfonylureas.
- Overall, the proportion of patients who were adherent to their initiated medication was significantly greater (P <.001) among patients who initiated SGLT-2 inhibitors than among patients who initiated sulfonylureas.
- The proportion of patients who were persistent with their index therapy was also significantly greater (P <.001) among patients who initiated SGLT-2 inhibitors than among patients who initiated sulfonylureas.
- Treatment initiation with an SGLT-2 inhibitor increased the likelihood of adherence by 36% and reduced the risk for treatment discontinuation by 25% versus initiation of a sulfonylurea.
- Further research is needed to determine if these findings correlate with better glycemic control and fewer complications in patients with type 2 diabetes.

is associated with damage to the eyes, kidneys, and nerves.[2] Type 2 diabetes is frequently managed through multimodal strategies, including diet and exercise, with a key focus on glycemic control.[3] The American Diabetes Association recommends lowering HbA_{1c} levels to <7% in most nonpregnant adults with diabetes, with a primary goal of reducing the risk for microvascular disease.[3]

According to current diabetes treatment guidelines, the recommended first-line pharmacologic treatment for type 2 diabetes is metformin.[3] For patients who do not achieve or maintain HbA_{1c} targets using metformin, or for patients who do not tolerate metformin, a therapeutic option is the addition of another antidiabetes medication class, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas, or thiazolidinediones.[3] Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are a relatively new class of medications indicated for the treatment of patients with type 2 diabetes. Canagliflozin, the first SGLT-2 inhibitor available in the United States, was approved by the US Food and Drug Administration (FDA) in March 2013; dapagliflozin was approved by the FDA in January 2014; and empagliflozin was approved shortly thereafter, in August 2014.

Historically, for patients who had been receiving monotherapy with metformin, sulfonylureas have been the most common add-on or replacement medication.[4] In a randomized, double-blind, active-controlled, 52-week, noninferiority trial, dapagliflozin had similar efficacy to the sulfonylurea glipizide as add-on therapy to metformin, and resulted in weight loss and reduced hypoglycemic events.[5] In a separate 52-week, double-blind, active-controlled noninferiority trial, patients who were inadequately controlled with metformin and received canagliflozin or the sulfonylurea glimepiride experienced different HbA_{1c} reductions, with canagliflozin 300 mg showing superiority to glimepiride.[6]

It is well-known that maintaining adherence to antidiabetes medication is vital to glycemic control and other favorable clinical outcomes, such as those examined in the clinical trials.[7] However, patient adherence to medications in observational studies or in real-world populations may differ from that observed in an experimental clinical trial setting where study participants are provided medications and have regular follow-up with study personnel.

To our knowledge, no analyses have compared real-world adherence and persistence between SGLT-2 inhibitors and sulfonylureas. Therefore, this study used a very large, contemporary, real-world population to compare medication adherence and persistence between patients with type 2 diabetes who were newly initiating an SGLT-2 inhibitor or a sulfonylurea.

Methods

This study used US administrative health insurance claims data extracted from the Truven Health MarketScan Commercial Claims and Encounters (Commercial), Medicare Supplemental and Coordination of Benefits (Medicare Supplemental), and Early View databases. These databases comprise enrollment information, demographic information, and inpatient medical, outpatient medical, and outpatient pharmacy claims data collected from more than 300 large, self-insured US employers and more than 25 health plans.

The Commercial database includes information for individuals who are insured through private health insurance plans. The Medicare Supplemental database includes information for individuals who are Medicare-eligible (primarily aged ≥65 years) and have supplemental health insurance paid for by their current or former employer. The Medicare Supplemental database includes the Medicare-paid and supplemental-paid components of reimbursed administrative claims. The Early View database includes all the components in the standard Commercial and Medicare Supplemental databases, but it has a short lag time and includes adjudicated claims for

Table 1 Patient Selection Criteria

Selection criteria	Patients using sulfonylurea, N (%)	Patients using SGLT-2 inhibitor, N (%)
Patients with ≥1 pharmacy claims for an SGLT-2 inhibitor or a sulfonylurea (including fixed-dose combinations) between January 1, 2015, and December 31, 2015 (earliest claim = index date; class of earliest medication = index class)[a]	470,284 (100.0)	151,514 (100.0)
Age ≥18 years at index date	470,157 (100.0)	151,469 (100.0)
Continuous enrollment in medical and pharmacy benefits for ≥12 months before the index date (baseline period)	371,836 (79.1)	124,367 (82.1)
Continuous enrollment in medical and pharmacy benefits for ≥6 months after the index date (follow-up period)	302,246 (64.3)	87,040 (57.4)
≥1 nondiagnostic medical claims[b] with a diagnosis code for type 2 diabetes in any position during the baseline period	280,717 (59.7)	82,542 (54.5)
No medical claims with a diagnosis code for type 1 diabetes during the baseline or follow-up periods	255,498 (54.3)	72,846 (48.1)
No medical claims with a diagnosis code for gestational diabetes during the baseline or follow-up periods	255,216 (54.3)	72,808 (48.1)
No medical claims with a diagnosis code for any pregnancy condition during the baseline or follow-up periods	253,453 (53.9)	72,092 (47.6)
No use of the index medication class during the baseline period	27,314 (5.8)	29,228 (19.3)
No use of the comparator medication class during the baseline period or on the index date	25,490 (5.4)	17,724 (11.7)
Final unmatched population	25,490 (5.4)	17,724 (11.7)

[a]Patients with more than 1 type of SGLT-2 inhibitor or sulfonylurea on the index date were excluded from the study.
[b]Claims that are not associated with a diagnostic workup used to rule out the presence of a condition, such as claims for laboratory tests.
SGLT-2 indicates sodium-glucose cotransporter 2.

healthcare services incurred up to 30 days before data extraction completion. Of the outpatient prescription claims, 97% are fully adjudicated within 30 days from the prescription fills. The databases used in this study contained data for more than 70 million unique individuals during the study period.

Study Design and Patient Selection Criteria

This was a retrospective, observational cohort study. **Table 1** outlines the patient selection criteria. Adults aged ≥18 years with ≥1 outpatient pharmacy claims for an SGLT-2 inhibitor or a sulfonylurea (including fixed-dose combinations) between January 1, 2015, and December 31, 2015, were selected from the databases. The date of the first outpatient pharmacy claim was designated the index date, and the medication class (ie, SGLT-2 inhibitors or sulfonylureas) initiated on the index date was designated the index medication class. Patients were required to have ≥12 months of continuous enrollment in medical and pharmacy benefits before the index date (ie, baseline period) and ≥6 months of continuous enrollment in medical and pharmacy benefits after the index date (ie, follow-up period).

In addition, patients were required to have a diagnosis of type 2 diabetes during the baseline period and to have no claims with diagnosis or procedure codes for type 1 diabetes, gestational diabetes, or pregnancy during the baseline or follow-up periods. To ensure that patients were naïve to their index medication class, patients were not allowed to have outpatient pharmacy claims for SGLT-2 inhibitors or sulfonylureas during the baseline period. Finally, patients with claims for an SGLT-2 inhibitor or a sulfonylurea on the index date and claims for more than 1 type of SGLT-2 inhibitor or more than 1 type of sulfonylurea on the index date were excluded.

Measurement of Adherence and Persistence

Medication adherence was measured using the proportion of days covered (PDC) by the index medication class during the 6-month follow-up period.[8] The PDC was calculated by dividing the number of days the patient was "covered" by the medication (ie, had the medication "on hand" according to the days of supply recorded on each prescription) during the follow-up period (numerator) by 180 days (denominator). If a patient had prescriptions for the medication class with overlapping days of supply (ie, if a patient refilled a prescription early), it was assumed that the patient completed the first prescription and started taking the second prescription on the day after completing the first; thus, the calculation extended the end of the days of supply of the second prescription by the number of days that it overlapped with the first prescription.

The PDC was computed across all medications within the index medication class (ie, individual medications within the SGLT-2 inhibitor class or the sulfonylurea class were considered interchangeable). The PDC had a value between 0% and 100% but was dichotomized at the clinically meaningful threshold of <80% versus ≥80%, which has been shown to be predictive of hospitalization and mortality among patients with diabetes taking oral antidiabetes medications.[9,10] Furthermore, the threshold of ≥80% PDC for antidiabetes medications

Table 2 Patient Demographics Measured as of Index Date

Demographics	Propensity score matched			Unmatched		
	Patients using sulfonylurea (N = 13,657)	Patients using SGLT-2 inhibitor (N = 13,657)	Standardized difference for matched cohorts, %	Patients using sulfonylurea (N = 25,490)	Patients using SGLT-2 inhibitor (N = 17,724)	*P* value for unmatched cohorts
Age, yrs, mean (SD)	54.3 (9.7)	54.3 (9.5)	0.522	57.7 (11.8)	54.0 (9.2)	<.001
Age-group						<.001
18-34 yrs	2.6%	2.5%	0.880	2.1%	2.4%	
35-44 yrs	12.6%	12.6%	0.229	10.2%	12.8%	
45-54 yrs	32.9%	32.2%	1.528	26.0%	33.6%	
55-64 yrs	42.6%	42.8%	0.572	39.4%	42.8%	
65-79 yrs	8.7%	9.3%	2.109	17.2%	7.9%	
≥80 yrs	0.6%	0.6%	0.692	5.0%	0.5%	
Men	53.9%	53.4%	1.005	56.1%	52.9%	<.001
Insurance plan type						<.001
Comprehensive	5.3%	5.4%	0.227	13.9%	4.5%	
EPO	0.5%	0.3%	2.691	0.4%	0.3%	
HMO	8.9%	8.9%	0.281	10.6%	8.4%	
POS	5.2%	5.1%	0.068	5.4%	5.1%	
PPO	60.2%	60.8%	1.078	53.1%	62.0%	
POS with capitation	0.4%	0.7%	3.647	0.3%	0.7%	
CDHP	11.0%	10.7%	0.813	8.7%	11.1%	
HDHP	3.7%	3.4%	1.556	3.3%	3.3%	
Unknown	4.9%	4.7%	0.909	4.3%	4.7%	
Payer						<.001
Commercial	90.0%	89.7%	1.043	77.0%	91.2%	
Medicare	10.0%	10.3%	1.043	23.0%	8.8%	
Geographic region						<.001
Northeast	17.0%	17.0%	0.125	16.3%	16.8%	
North Central	16.6%	16.9%	0.739	23.4%	15.8%	
South	58.3%	57.8%	1.143	49.7%	59.9%	
West	7.9%	8.2%	1.320	10.6%	7.5%	
Unknown	0.2%	0.1%	0.637	0.1%	0.1%	
Population density						.022
Urban	83.7%	83.8%	0.344	83.3%	84.3%	
Rural	16.2%	16.1%	0.236	16.6%	15.7%	
Unknown	0.1%	0.1%	1.334	0.1%	0.1%	
Index copay, mean (SD)[a]	$4 ($6)	$48 ($70)	88.163	$4 ($6)	$48 ($83)	<.001

[a]Not used in the propensity score model.

CDHP indicates consumer-directed health plan; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; SD, standard deviation; SGLT-2, sodium-glucose cotransporter 2.

is used by the Centers for Medicare & Medicaid Services as a quality measure for Part D Star Ratings.[11]

Persistence with the index medication class was measured as the number of days from the index date until the earliest of a discontinuation of the index medication class or the end of follow-up. Medication discontinuation was defined as a gap in therapy with the index medication class of >60 days. Like adherence, persistence was calculated across all medications within the index medication class.

Measurement of Covariates

The covariates included the patients' demographic

Table 3 Patient Clinical Characteristics Measured During 12-Month Baseline Period

Clinical characteristics	Propensity score matched			Unmatched		
	Patients using sulfonylurea (N = 13,657)	Patients using SGLT-2 inhibitor (N = 13,657)	Standardized difference for matched cohorts, %	Patients using sulfonylurea (N = 25,490)	Patients using SGLT-2 inhibitor (N = 17,724)	*P* value for unmatched cohorts
Deyo-Charlson Comorbidity Index, mean (SD)	1.7 (1.3)	1.7 (1.3)	2.560	2.0 (1.6)	1.7 (1.3)	<.001
Adapted Diabetes Complications Severity Index, mean (SD)	0.7 (1.2)	0.7 (1.2)	2.115	0.9 (1.5)	0.7 (1.2)	<.001
Number of unique 3-digit *ICD-9-CM* diagnosis codes,[a] mean (SD)	10.7 (7.0)	10.8 (6.8)	1.549	11.3 (8.0)	10.9 (6.8)	<.001
Number of unique NDC codes, mean (SD)	12.5 (8.4)	12.7 (7.9)	2.994	11.5 (8.3)	13.6 (8.2)	<.001
Total healthcare expenditures, mean (SD)	$12,295 ($23,921)	$12,824 ($23,580)	2.228	$15,096 ($38,103)	$13,670 ($22,526)	<.001
Endocrinologist visit	10.2%	12.2%	6.439	6.6%	17.3%	<.001
Microvascular complications of diabetes	16.3%	17.4%	2.939	18.0%	19.1%	<.001
Diabetic nephropathy	3.2%	3.5%	1.604	4.5%	3.7%	<.001
Diabetic retinopathy	6.5%	7.0%	2.076	6.8%	7.9%	<.001
Diabetic peripheral neuropathy	9.0%	9.6%	1.860	9.5%	10.6%	<.001
Macrovascular complications of diabetes	14.3%	14.6%	0.881	20.7%	14.6%	<.001
Atherosclerosis	11.3%	11.5%	0.535	16.0%	11.7%	<.001
Stroke	1.1%	1.1%	0.191	2.3%	1.0%	<.001
Myocardial infarction	0.8%	0.8%	0.110	1.6%	0.8%	<.001
Unstable angina pectoris	0.9%	0.8%	0.433	1.4%	0.7%	<.001
Heart failure	2.2%	2.3%	0.674	4.9%	2.1%	<.001
Percutaneous coronary intervention	0.9%	0.8%	0.887	1.2%	0.7%	<.001
Coronary artery bypass graft	0.3%	0.2%	0.835	0.4%	0.2%	<.001
Peripheral vascular disease	2.4%	2.6%	1.213	4.0%	2.5%	<.001
Other comorbidities						
Renal impairment	6.4%	6.8%	1.974	11.4%	6.5%	<.001
Hypertension	76.3%	76.5%	0.518	76.8%	77.3%	.223
Dyslipidemia	79.2%	79.5%	0.716	75.1%	81.6%	<.001
Depression	8.5%	8.4%	0.288	8.1%	8.7%	.028
Hypoglycemia	2.9%	3.1%	1.182	3.1%	3.2%	.347
Proteinuria	1.9%	1.9%	0.439	2.0%	2.0%	.706
Antihypertensive medications						
Renin-angiotensin system antagonists	65.6%	65.8%	0.421	60.6%	68.4%	<.001
ACE inhibitors	42.5%	42.0%	0.850	40.7%	43.0%	<.001
ARBs	25.7%	26.4%	1.504	22.1%	28.3%	<.001
Direct renin inhibitors	0.2%	0.2%	0.000	0.1%	0.2%	.227
Diuretics	35.4%	35.5%	0.272	35.0%	36.3%	.006
Other antihypertensives	34.8%	34.9%	0.294	37.9%	35.0%	<.001
Number of antidiabetes medication classes, mean (SD)	1.2 (0.8)	1.3 (0.8)	7.250	1.0 (0.7)	1.5 (0.9)	<.001

Continued

Table 3 Patient Clinical Characteristics Measured During 12-Month Baseline Period *(Continued)*

Clinical characteristics	Propensity score matched			Unmatched		
	Patients using sulfonylurea (N = 13,657)	Patients using SGLT-2 inhibitor (N = 13,657)	Standardized difference for matched cohorts, %	Patients using sulfonylurea (N = 25,490)	Patients using SGLT-2 inhibitor (N = 17,724)	*P* value for unmatched cohorts
Antidiabetes medication use in baseline period						
Alpha-glucosidase inhibitors	0.3%	0.2%	0.409	0.2%	0.3%	.104
Metformin	75.4%	74.7%	1.595	65.1%	76.5%	<.001
DPP-4 inhibitors	26.5%	28.0%	3.392	18.3%	30.9%	<.001
Meglitinides	1.0%	1.1%	0.391	0.8%	1.4%	<.001
TZDs	5.7%	6.0%	1.579	4.1%	7.6%	<.001
Insulins	14.8%	17.8%	8.026	9.4%	26.9%	<.001
GLP-1 receptor agonists	7.8%	10.4%	8.840	4.4%	17.7%	<.001
Amylin analogs	0.0%	0.1%	4.474	0.0%	0.1%	<.001
Concurrent antidiabetes medication use						
Alpha-glucosidase inhibitors	0.0%	0.0%	0.856	0.0%	0.0%	.706
Metformin	78.4%	77.2%	3.083	77.1%	75.5%	<.001
DPP-4 inhibitors	5.8%	6.3%	2.033	4.0%	7.0%	<.001
Meglitinides	0.3%	0.3%	0.549	0.2%	0.3%	.066
TZDs	1.4%	1.6%	1.438	1.0%	2.2%	<.001
Insulins	2.9%	4.0%	5.985	1.8%	7.3%	<.001
GLP-1 receptor agonists	1.2%	1.9%	5.466	0.7%	3.2%	<.001
Amylin analogs	0.0%	0.0%	—	0.0%	0.0%	.168
Any mail-order prescription[b]	13.0%	13.1%	0.326	17.3%	12.5%	<.001

[a]The baseline period for all patients occurred before the implementation of the *International Classification of Diseases, Tenth Revision* coding.

[b]Mail-order prescription was measured during the follow-up period.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification*; NDC, National Drug Code; SD, standard deviation; SGLT-2, sodium-glucose cotransporter 2; TZD, thiazolidinedione.

and clinical characteristics, which were measured to describe the study sample and for use in the propensity score models. The patients' demographics were measured on the index date using health insurance enrollment records, and are shown in **Table 2**. The clinical characteristics were measured throughout the 12-month baseline period, and are shown in **Table 3**.

The Deyo-Charlson Comorbidity Index[12]; the number of unique 3-digit *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes[13]; the number of unique National Drug Codes[13]; and the total healthcare expenditures were captured as measures of overall health. The diabetes-related characteristics included the adapted Diabetes Complications Severity Index,[14] the presence of a visit to an endocrinologist, and diagnoses and procedures that are indicative of the macrovascular and microvascular complications of diabetes.

Medication use was also captured, including baseline use of antihypertensive and antidiabetes medications, as well as concurrent use of antidiabetes medications, because previous antidiabetes medication use and polypharmacy may be indicative of type 2 diabetes that is difficult to manage and shows greater medication burden. The concurrent use of antidiabetes medications was determined based on a previously published algorithm evaluating the overlapping use of the index medication and other antidiabetes medications immediately before and after the index date.[15]

Statistical Analyses

Bivariate descriptive analyses were conducted on the unmatched and propensity score–matched samples. Categorical variables were compared between the cohorts using chi-square tests. Continuous variables were compared between the cohorts using *t*-tests.

Propensity score matching was conducted to reduce the potential for confounding that was introduced by differences in the measured demographic and clinical characteristics between the SGLT-2 inhibitor and sulfonylurea cohorts. Propensity scores were estimated using a logistic regression model, with the dependent variable being a binary indicator for membership in the SGLT-2 inhibitor

Table 4 Adherence and Persistence Outcomes Measured During 6-Month Follow-Up Period

Demographics	Propensity score matched			Unmatched		
	Patients using sulfonylurea (N = 13,657)	Patients using SGLT-2 inhibitor (N = 13,657)	*P* value for matched cohorts	Patients using sulfonylurea (N = 25,490)	Patients using SGLT-2 inhibitor (N = 17,724)	*P* value for unmatched cohorts
PDC by index medication class (adherence),[a] mean (SD)	71.8% (29.3%)	75.6% (27.5%)	<.0001	72.1% (29.6%)	75.8% (27.3%)	<.001
PDC ≥80%	53.9%	61.4%	<.0001	54.7%	61.8%	<.001
Nonpersistent with index medication class[b]	31.1%	23.9%	<.0001	31.4%	23.6%	<.001
Days to nonpersistence among patients who discontinued, mean (SD)	80.7 (50.8)	77.0 (48.7)	<.0001	80.6 (50.3)	77.2 (48.6)	<.001

[a]Proportion of days covered calculated as the number of days with index medication class "on hand" divided by 180 days and capped at 100%.
[b]Nonpersistent is defined as the presence of a >60-day gap past the end of the previous fill's days' supply (fill date plus days' supply).
PDC indicates proportion of days covered; SD, standard deviation; SGLT-2, sodium-glucose cotransporter 2.

cohort, and a group of independent variables comprising the patient demographic and clinical characteristics listed in Tables 1 and 2 (except the index copay, which was considered a characteristic of the index medication).

Once the propensity score was estimated, patients receiving an SGLT-2 inhibitor were matched to patients receiving a sulfonylurea at a 1:1 ratio.[16] The balance in patient characteristics achieved by the propensity score matching was assessed with the standardized difference.[17] A standardized difference of <10% was considered an adequate match.[18,19]

Ultimately, a bivariate logistic regression model was used to compare the odds of achieving the PDC ≥80% threshold between the matched SGLT-2 inhibitor and sulfonylurea cohorts, and a bivariate Cox proportional hazards regression model was used to compare the hazards of medication discontinuation between the matched SGLT-2 inhibitor and sulfonylurea cohorts.

Results

In 2015, there were 151,514 patients with ≥1 claims for an SGLT-2 inhibitor and 470,284 patients with ≥1 claims for a sulfonylurea in the 3 databases combined. After applying the study inclusion and exclusion criteria, the final unmatched sample comprised 17,724 initiators of an SGLT-2 inhibitor and 25,490 initiators of a sulfonylurea (Table 1). Before matching, the sulfonylurea cohort was significantly older, on average, and had a significantly larger proportion of men, in addition to having other demographic differences compared with the SGLT-2 inhibitor cohort (Table 2).

Compared with SGLT-2 inhibitor initiators, sulfonylurea initiators had significantly higher average Deyo-Charlson Comorbidity Index scores, significantly higher total baseline healthcare expenditures, and a significantly greater proportion of patients with macrovascular diabetes complications (Table 3). A significantly lower proportion of patients in the sulfonylurea cohort had a baseline visit to an endocrinologist compared with the SGLT-2 inhibitor cohort.

For both cohorts, the most common antidiabetes medications used during the baseline period were metformin, DPP-4 inhibitors, and insulin. The use of all 3 medications was significantly less common among sulfonylurea initiators than among SGLT-2 inhibitor initiators. A large proportion of both cohorts was receiving metformin concurrently with their index drug on their index date.

After propensity score matching, 13,657 patients were in each cohort. Adequate balance was achieved on the covariates included in the propensity score model, as evidenced by standardized differences of <10% (Tables 2 and 3). On average, the matched cohorts were aged 54 years, and nearly 54% were men. Approximately 75% of the matched patients received metformin during the baseline period, and just more than 25% received a DPP-4 inhibitor.

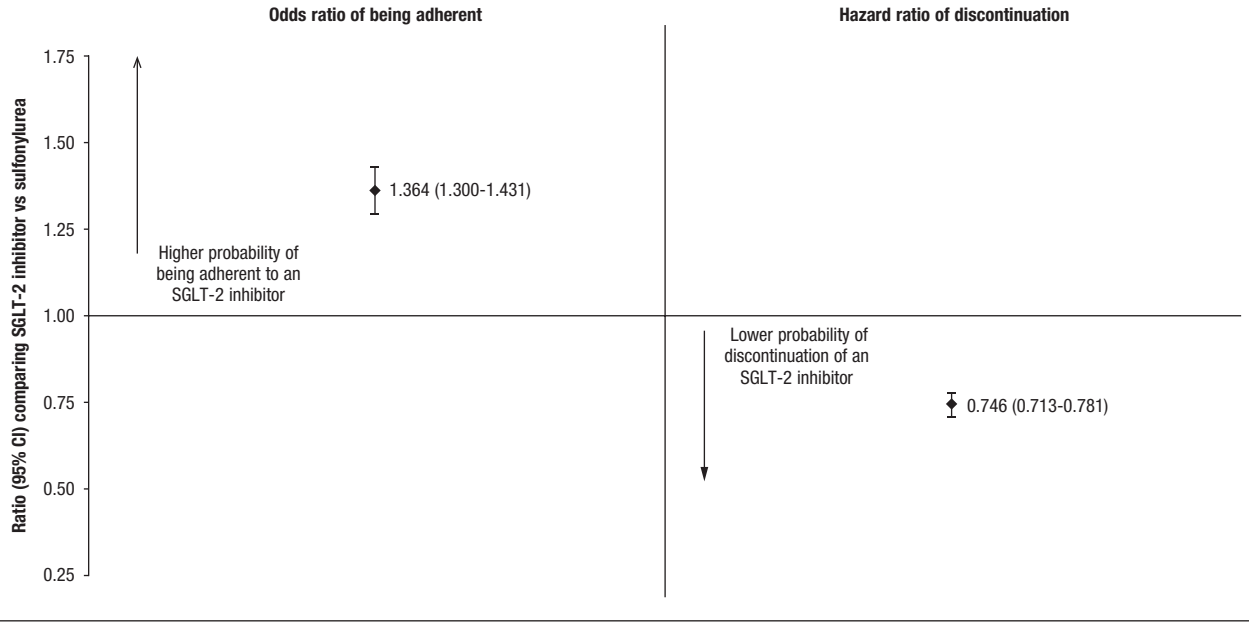
Among matched patients, the average PDC during the 6-month follow-up period was significantly lower for sulfonylurea initiators than for SGLT-2 inhibitor initiators (71.8% vs 75.6%, respectively; *P* <.0001; **Table 4**). Similarly, the proportion of patients classified as adherent was significantly lower in the sulfonylurea cohort than in the SGLT-2 inhibitor cohort (53.9% vs 61.4%, respectively), with a corresponding odds ratio of 1.364 (*P* <.0001; **Figure**).

A significantly larger proportion of patients receiving a sulfonylurea than patients receiving an SGLT-2 inhibitor discontinued their index medication class during follow-up (31.1% vs 23.9%, respectively; *P* <.0001). In a Cox proportional hazards model fit on the matched patient sample, patients who received an SGLT-2 inhibitor had 25% lower hazards of discontinuing their treatment than patients receiving a sulfonylurea (0.746; *P* <.0001).

Discussion

This claims-based study compared propensity score–

Figure Odds Ratio of Being Adherent, Hazard Ratio of Medication Discontinuation During 6-Month Follow-Up Period After Matching



CI indicates confidence interval; SGLT-2, sodium-glucose cotransporter 2.

matched populations of adults with type 2 diabetes initiating SGLT-2 inhibitors or sulfonylureas. In this analysis, patients who were newly initiating an SGLT-2 inhibitor were 36% more likely to be adherent to their medication and 25% less likely to discontinue their medication than patients who initiated a sulfonylurea. Given the large number of antidiabetes medications available in the United States and the importance of adherence and persistence, real-world research comparing and differentiating between medication classes in terms of compliance is important. This analysis adds to the body of literature from clinical trials comparing SGLT-2 inhibitors and sulfonylureas.

Several published analyses have compared adherence and persistence between sulfonylureas and other classes of antidiabetes medication. Patients using sulfonylureas have been shown to have poorer persistence compared with those receiving DPP-4 inhibitors in a German study of primary care practices[20] and in a US claims-based study.[15] Another claims-based study comparing the DPP-4 inhibitor sitagliptin with sulfonylureas as an add-on therapy to metformin showed that patients adding a sulfonylurea had lower adherence and persistence than patients adding sitagliptin.[21]

A Canadian analysis showed that patients newly initiating a sulfonylurea had a greater likelihood of discontinuing their antidiabetes medication and a lower likelihood of starting another antidiabetes medication after their first treatment compared with patients initiating metformin.[22] Poorer persistence for patients receiving a sulfonylurea compared with patients receiving metformin was also reported in an Irish claims analysis.[23] By contrast, SGLT-2 inhibitors have been associated with better adherence and persistence than DPP-4 inhibitors and glucagon-like peptide-1 receptor agonists in US claims analyses.[24,25] The results of these other published studies are consistent with the analysis presented here.

Adherence and persistence are often compared between antidiabetes medications and/or medication classes because of the association between adherence to antidiabetes medications and improved outcomes. A 2011 review article identified 37 published articles that examined the association between adherence to antidiabetes medication and several health outcomes.[7] Of those studies, 22 used pharmacy claims or refill records to measure adherence.[7] Asche and colleagues found that better adherence was associated with better glycemic control.[7] Glycemic control is important in diabetes management to prevent microvascular disease.[3] The previously cited review article also showed that better adherence to antidiabetes medications was associated with decreased healthcare utilization.[7]

Asche and colleagues reported that the association between better antidiabetes medication adherence and decreased healthcare costs is less clear,[7] although some analyses have reported a significant relationship between the two, with better adherence associated with lower costs.[26-28]

Although the benefits of adherence to antidiabetes medications are well-documented, adherence remains a challenge for many patients. In this analysis, a little more than 50% of the patients were considered adherent, which was defined as having PDC ≥80%. Additional research to determine the modifiable drivers of nonadherence and nonpersistence and to test potential adherence interventions among adults with type 2 diabetes is needed.

Limitations

This research has limitations. Administrative claims are generated for billing purposes, not for research. It was assumed that patients took their medications for the duration of the days of supply on the medication claim.

Certain patient characteristics that may affect provider prescribing decisions or influence adherence and persistence were not available in the databases. These characteristics include race, socioeconomic status, glycemic control, weight, physical activity, and family history. If these differed by cohort after matching and are associated with adherence and persistence, the study findings may be biased.

In addition, reasons for medication discontinuation are not available in the data.

Finally, this analysis did not attempt to associate adherence and persistence with clinical outcomes.

Conclusions

In this retrospective analysis using real-world data, we found that adults with type 2 diabetes who initiated an SGLT-2 inhibitor medication had better adherence and persistence than patients who initiated a sulfonylurea medication. Further research is needed to determine if the better adherence and persistence associated with taking an SGLT-2 inhibitor translates into better glycemic control and fewer complications in patients with type 2 diabetes. ■

Author Disclosure Statement

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STAKEHOLDER PERSPECTIVE

Real-World Studies in Diabetes Needed to Improve Medication Adherence and Persistence

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Diabetes is one of the main cost drivers of our unsustainably expensive healthcare system. Real-world studies, such as the one by Bell and colleagues,[1] are important to understand how patients navigate the system, and to optimize treatments for better clinical and economic outcomes.

PATIENTS: Living with diabetes does not begin and end with the clinical encounter: it is a 24/7 commitment. Several relatively new therapeutic classes of antidiabetes medications are available that provide more treatment choices. Recent evidence suggests that in non–insulin-treated patients with type 2 diabetes, there may be no need to perform self-monitoring of blood glucose, which could save valuable time, pain, and mental anguish for patients.[2]

Bell and colleagues were not able to determine the reasons for medication discontinuation from the claims data.[1] Only approximately 50% of the patients in the study were adherent; side effects and cost might have led patients to become nonadherent or to lack persistence. Drug copay coupons and other market distortions can result in brand-name medications being available to the patient at no cost at the pharmacy counter, but these mechanisms may increase the total costs for the healthcare system.

PHYSICIANS: Physicians focus on providing the highest quality of care they can, and they need real-world evidence to advise their patients with diabetes on best treatments. Sodium-glucose cotransporter (SGLT)-2 inhibitors and other new classes of antidiabetes medications are promising, because they generally are not associated with the risk for hypoglycemic episodes that sulfonylureas may have. However, the US Food and Drug Administration has added a boxed warning to the SGLT-2 inhibitors prescribing information because of the potential of doubling the risk for leg and foot amputations with at least 1 of these agents,[3] as is done in Europe.

Thus, more studies are warranted to evaluate the clinical outcomes of SGLT-2 inhibitors. In addition, because Medicare and commercial payers are focusing on moving physicians and health systems to value-based payment methods, physicians will need to be more mindful of the total cost of care they deliver, including the cost of medications they prescribe to their patients. Because most patients with diabetes are receiving more than 1 medication and have several comorbidities, knowing who is nonadherent, and why, will help target outreach to patients who need extra assistance.

PAYERS: Payers and their customers are focused on preventing diabetes, slowing its progression, and improving the clinical and economic outcomes of members who have this disease. Because we do not have any generic insulin preparations, the new classes of antidiabetes medications provide more options for effective treatment. Metformin use is not optimized and can be improved, and multiagent protocols are becoming more common. The SGLT-2 inhibitor list prices are more than 100 times the average cost of metformin and sulfonylureas. We do not yet have data suggesting that they also have that margin in improved effectiveness. However, medications that are not taken cannot help the patient; we therefore need more real-world studies, such as the one by Bell and colleagues, to improve the treatment regimens for diabetes. ■

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